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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/383,894	08/26/1999	MING LI	004.00191	7158

35876 7590 01/13/2004

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EXAMINER
LACOURCIERE, KAREN A

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/383,894	LI, MING	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 22 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet* .

Continuation of Attachment(s) 6). Other: Receipt date for Endocrinology Vol. 138, No. 9.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07-11-2003 has been entered.

Drawings

The drawings were received on 07-11-2003. These drawings are acceptable.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 49 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 49 is drawn to methods wherein the pancreatic beta cells are in a subject with type II diabetes; however, claim 49 depends from claim 43, which indicates that the cells are pancreatic beta cells are in vitro. It is unclear how pancreatic beta cells can be in vitro, but also in a subject with type II diabetes.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 49 is maintained as rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the prior Office action (mailed 09-12-00), because the specification, while being enabling for modifying beta cell insulin secretion using known calcium channel blockers, does not reasonably provide enablement for modifying beta cell insulin secretion using any calcium channel blocker or inhibitor of channel formation, ribozyme, antisense or an expressed gene *in vivo* in beta cells present in a subject having type II diabetes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claim 49 is drawn broadly to methods of modulating insulin secretion in pancreatic beta cells by modifying levels of functional T-type calcium channels by any mechanism, including modulating insulin secretion *in vivo* (whole organism) in

pancreatic beta cells present in a subject having type II diabetes, including wherein the modifying levels of functional T-type calcium channels is performed using antisense or expressing a nucleic acid encoding a T-type calcium channel.

The specification provides examples wherein T-type calcium channel blockers, including mibefradil and $NiCl_2$ are administered to pancreatic cells, *in vitro* (cell culture) and T-type calcium channel activity is blocked. There are no examples provided in the instant specification wherein an inhibitor of channel formation, an antisense molecule, a ribozyme or an expressed pancreatic T-type calcium channel are demonstrated to alter insulin secretion in beta cells in any setting, including *in vitro*. Further, there are no examples provided by the instant specification wherein an antisense molecule or a ribozyme are demonstrated to alter the level of a T-type calcium channel or alter the expression of a nucleic acid encoding a T-type calcium channel in any setting, including *in vitro*. There are no examples provided wherein levels of functional T type calcium channels are modified in an individual with type II diabetes by any means.

At the time the instant invention was made, modifying insulin secretion in beta cells in vivo (whole organism), including in a subject with type II diabetes, via calcium channel blockers was unpredictable (see for example Verma, S. et al. page 126), calcium channel blockers reported to inhibit insulin secretion *in vitro* do not predictably produce the same effect *in vivo*. The reason for this variability was unknown, and one skilled in the art would not be able to predict what calcium channel blockers would modify insulin secretion *in vivo* (whole organism), based on *in vitro* screening.

Further, the claimed methods read on *in vivo* (whole organism) methods of modifying insulin secretion using nucleic acid based drugs, including antisense, ribozymes and gene therapy methods in a subject with type II diabetes. At the time the instant invention was made, and even now, *in vivo* (whole organism) methods using

antisense, ribozymes and gene therapy were highly unpredictable (see, for example, Branch, Agrawal, Rossi, Anderson and Verma, I. et al.) due to issues including the determination of accessible target regions, how to specifically deliver an antisense molecule, ribozyme or gene therapy vector to a target cell at a concentration effective to result in a desired effect, and, in the case of gene therapy, the determination of target cell specific vectors and promoters to achieve and maintain expression of the gene.

The specification, as filed, provides only general guidance with regard to such factors. Due to the unpredictability in the art, the field to date does not have guidelines that would enable one skilled in the art to routinely practice methods drawn to *in vivo* applications of antisense, ribozymes and gene therapy. As such, one skilled in the art would need to determine such factors de novo, through empirical, undue trial and error experimentation. The skilled artisan would need to first determine what compounds interfere with T-type calcium channel pore formation and what ribozyme and antisense sequences are able to inhibit the expression of a nucleic acid encoding a pancreatic T-type calcium channel, *in vivo* or *in vitro*. Further, one skilled in the art would need to determine which of these compounds change the level of functional t-type calcium channels in a manner and to the degree that insulin secretion would be modified. Additionally, one skilled in the art would need to determine how to deliver antisense molecules, ribozymes or gene therapy vectors specifically to pancreatic beta cells, in vivo, at a concentration which is effective to change the level of functional t-type calcium channels, and modify insulin secretion in said beta cells. This would include the determination of such factors as dosage, route of administration, disposition of the antisense molecule in tissues, and the half life and stability of the antisense or ribozyme molecule *in vivo*. For gene therapy, in particular, it would require the determination of an appropriate vector and enhancer-promoter combination for beta-cells “the search for

such combinations is a case of trial and error for a given type of cell."(see Verma, for example p 240, columns 2 and 3) in order to get a high and sustained expression of a t-type calcium channel, such that beta cell insulin secretion would be modified.

Therefore, based on the breadth of the claims, the nature of the invention, the state of the art, the high level of unpredictability in the art, the lack of specific guidance by the inventor, the lack of working examples, and the quantity of experimentation that would be required, it would require undue experimentation, beyond what is taught in the specification, to practice the methods as claimed, over the full scope claimed.

Claims 43-49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not provide sufficient written description of an adequate number of species of compounds that modify T type calcium channel levels such that the skilled artisan would recognize that the inventors has possession of the genus of compounds to modify levels of functional T type calcium channels, including modifying levels of T type calcium by modifying the expression levels of T type calcium channel genes. The specification discloses two small molecule inhibitors of T type calcium channels, $NiCl_2$ and mibefradil, and the prior art discloses streptozocin. Further, the specification discloses that the rat neuronal T type calcium channel has been cloned, which provides written description of antisense to the rat T type neuronal calcium channel and gene therapy vectors comprising the rat gene, however, the specification

also discloses that "Other subunits of T-type Ca^{2+} channel have yet to be identified" (see page 3 of the instant specification, first paragraph). Claims 43-49 are directed to encompass methods that utilize, for example, gene sequences, ribozymes and antisense sequences from species other than rat and subunits which were not identified at the time of filing. None of these sequences, or antisense or ribozymes and other inhibitors meet the written description provision of 35 USC 112, first paragraph. Further, it would encompass small molecule inhibitors, antibodies, etc., that bind and inhibit other subunits of T-type calcium channels which were not even identified at the time of filing. The specification provides insufficient written description to support the genus encompassed by the claim. The skilled artisan would not be able to envision the structure of the genus of modification compounds, particularly gene sequence based modifiers, such as gene therapy sequences and antisense, based on the small number of species disclosed in the specification and the prior art, because the structures of such compounds are highly variant (e.g. nucleic acid sequence).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the rat neuronal T type calsium channel, mibefradil, $NiCl_2$ and streptozocin, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, antibodies, small molecules, etc. required to practice the claimed methods, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were

found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.
>
> The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

Therefore, the full breadth of the claims does not meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded

that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Claim Rejections - 35 USC § 102

The rejection of record of claims 43 and 47 under 35 U.S.C. 102(b) as being anticipated by Verma, S. et al. is withdrawn in response to Applicant's amendments filed 07-11-203, which limits the claims to in vitro inhibition.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 43 and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Bhattacharjee et al. for the reasons of record set forth in the prior Office action (mailed 09-12-00). The rejection of record is set forth as follows.

Bhattacharjee et al. disclose a method wherein rat beta cells (INS-1) are contacted *in vitro* (cell culture) with $NiCl_2$, with a dose dependent reduction in glucose stimulated insulin secretion. It is noted that the publication date of Bhattacharjee et al. is less than one year before the filing date of the instant application, however, the public availability date of Bhattacharjee et al. is more than one year prior to the filing date (see date of receipt in the PTO library, attached) and, therefore, Bhattacharjee et al. qualifies as prior art under 35 USC 102(b).

Therefore, Bhattacharjee et al. anticipates claims 43 and 47.

Claim 43 is maintained as rejected under 35 U.S.C. 102(b) as being anticipated by Kato et al.

Kato et al. disclose a method wherein neonatal rats are treated with streptozocin, increasing the level of functional T-type calcium channels; evidenced by the increased Ba^{2+} induced currents, and increasing insulin secretion. This modification of levels of T-type calcium channels and insulin secretion was maintained in these cells when cultured in vitro.

Therefore Kato et al. anticipates claim 43.

Response to Arguments

Applicant's arguments filed 07-11-2003 have been fully considered but they are not persuasive. In response to the rejection of record of claims 43 and 47 under 35 USC 102(a), as anticipated by Bhattacharjee et al., Applicant argues that Bhattacharjee et al. is a reference by Applicant published less than one year prior to filing and, therefore, is not available as prior art. This is not found to be persuasive because Bhattacharjee et al. is a prior art reference by others, i.e. the reference includes authors in addition to the one named inventor of the instant application. Further, the prior art reference Bhattacharjee et al. was publicly available more than one year before the filing of the instant application, as evidenced by the attachment showing receipt of Endocrinology Vol 138, No.9 at the PTO library on August 21, 1997, and therefore qualifies as prior art under 35 USC 102(b).

In response to the rejection of record of claim 43 under 35 USC 102(b) as anticipated by Kato et al. Applicant argues that Kato et al. teach away from the claimed invention because Kato et al. state that the role of T-Type Ca^{2+} channels excitation-secretion pathway coupling of beta cells is unknown.

These arguments have been fully considered, however, not found to be persuasive because the reference Kato et al. is an anticipatory reference. Kato et al. discloses the same method as instantly claimed, whether or not the mechanism was appreciated by Kato et al. and, therefore, anticipates the claimed method.

Claim Objections

Claim 49 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 49 is drawn to a method wherein pancreatic beta cells are in a subject having type II diabetes, however, claim 49 depends from claim 43, which is drawn to a method wherein pancreatic beta cells are in vitro, therefore, it does not appear that claim 49 limits the method of claim 43.

Conclusion

Any rejection of record not repeated herein is considered to be withdrawn.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication should be directed to Karen A. Lacourciere at telephone number (703) 308-7523. The Examiner can normally be reached Monday-Thursday from 7:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at (703) 308-0447. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere

October 23, 2003

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER